

Claims

1. A method to predict which patients will respond to a tyrosine kinase inhibitor drug in Philadelphia chromosome positive leukemia patients comprising:
 - a) determining RNA expression levels in blood for a plurality of the 55 reporter genes shown in Tables 12A and 12B;
 - b) comparing patients gene expression profile to the mean complete cytogenetic response expression profiles shown in Tables 12A and 12B;
 - c) determining the Pearson correlation coefficient resulting from the comparison in (b);
 - d) determining that the patient will have complete cytogenetic response to the tyrosine kinase inhibitor if the correlation coefficient is equal to or greater than 0.57; and
 - e) determining that the patient will be a non-responder if the correlation coefficient is less than 0.57.
2. A method to predict which patients will respond to a tyrosine kinase inhibitor drug in Philadelphia chromosome positive leukemia patients comprising:
 - a) determining RNA expression levels in blood for a plurality of the 55 reporter genes shown in Tables 12A and 12B;
 - b) comparing patients gene expression profile to the mean complete cytogenetic response expression profiles shown in Tables 12A and 12B;
 - c) determining the Pearson correlation coefficient resulting from the comparison in (b);
 - d) determining that the patient will have complete cytogenetic response to the tyrosine kinase inhibitor if the correlation coefficient is equal to or greater than 0.54; and

- e) determining that the patient will be a non-responder if the correlation coefficient is less than 0.54.
3. The method of claim 1 or 2, wherein the plurality of the 55 reporter genes comprises two or more of the 55 reporter genes shown in Tables 12A and 12B.
 4. The method of any of claims 1 to 3, wherein the tyrosine kinase inhibitor is Imatinib mesylate (Imatinib or GLEEVEC® or GLIVEC® or STI571).
 5. The method of any of claims 1 to 4, wherein only the 31 reporter genes in Table 12A are used.
 6. A method for determining the responsiveness of an individual with Philadelphia chromosome positive leukemia to treatment with a tyrosine kinase inhibitor drug comprising:
 - a) determining for the two copies of the CSK gene, present in the individual, the identity of the nucleotide pair at the polymorphic site at position 36211 of sequence AC020705.4; and
 - b) assigning the individual to a good responder group if both pairs are AT, or if one pair is AT and one pair is GC, and to a low responder group if both pairs are GC.
 7. A method for determining the responsiveness of an individual with Philadelphia chromosome positive leukemia to treatment with a tyrosine kinase inhibitor drug comprising:
 - a) determining for the two copies of the CYP1A1 gene, present in the individual, the identity of the nucleotide pair at the polymorphic site at position 6819 in sequence X02612; and
 - b) assigning the individual to a good responder group if both pairs are AT, and to a poor responder group if both pairs are GC, or if one is GC and one is AT.
 8. A method for determining the responsiveness of an individual with Philadelphia chromosome positive leukemia to treatment with a tyrosine kinase inhibitor drug comprising:

- a) determining for the two copies of the IL-1 β gene, present in the individual, the identity of the nucleotide pair at position 1423 of sequence X04500; and
 - b) assigning the individual to a good responder group if both pairs are CG, and to a poor responder group if one pair is AT and one pair is CG or if both pairs are AT.
9. The method of claims 6, 7 or 8, wherein the tyrosine kinase inhibitor is Imatinib mesylate (Imatinib or GLEEVEC® or GLIVEC® or STI571).
 10. A method to determine the probability of a positive clinical response in a patient, with a tyrosine kinase inhibitor drug responsive disorder, to treatment with a tyrosine kinase inhibitor drug; comprising:
 - (a) obtaining a biological sample from the said patient,
 - (b) determining the levels of gene expression of two or more of the 55 reporter genes listed in Tables 12A and 12B in the sample from the patient, and
 - (c) comparing the levels of gene expression of the two or more genes determined in (b) to the levels of expression of the same genes as listed in Tables 12A and/or 12B and
 - (d) determining the degree of similarity between the levels of gene expression of the two or more genes determined in (c), and
 - (e) determining from the degree of similarity between the levels of gene expression of the two or more genes the probability that the patients will respond to a tyrosine kinase inhibitor drug .
 11. The method of claim 10 wherein the tyrosine kinase inhibitor drug responsive disorder is Philadelphia chromosome positive leukemia.
 12. The method of claim 11 or 11, wherein the tyrosine kinase inhibitor is Imatinib mesylate (Imatinib or GLEEVEC® or GLIVEC® or STI571).

13. The method of any of claims 10 to 12 , wherein the biological sample is selected from the group consisting of; a tissue biopsy, blood, serum, plasma, lymph, ascitic fluid, cystic fluid, urine, sputum, stool, saliva, bronchial aspirate, CSF or hair.
14. A method according to claim 13, wherein the biological sample is a tissue biopsy cell sample or cells cultured therefrom.
15. A method according to claim 13 or 14, wherein the tissue biopsy is a biopsy of bone marrow or solid tissue.
16. A method according to any of claims 13 to 15, wherein the tissue biopsy comprises cells removed from a solid tumor.
17. A method according to claim 13 or 14, wherein the biological sample are blood cells.
18. A method according to any of claims 13 to 17, wherein said sample is a lysate of said cell sample.
19. The method of any of claims 10 to 18, wherein the level of gene expression is determined by measuring the level of transcription of the two or more genes in Tables 12A and/or 12B.
20. The method of claim 19 wherein the level of transcription is determined by measuring the level of mRNA of the two or more genes in Tables 12A and/or 12B.
21. The method of claim 19, wherein the level of transcription is determined by measuring the level of cDNA corresponding to the two or more genes in Tables 12A and/or 12B.
22. The method of any of claims 19 to 21, wherein the step of measuring further comprises amplifying the mRNA or cDNA.
23. The method of any of claims 19 to 22, wherein the level of transcription is determined by techniques selected from the group of Northern blot analysis, reverse transcriptase PCR, real-time PCR, RNase protection, and microarray.

24. The method of any of claims 10 to 23, wherein the level of gene expression is determined for a plurality of the 55 reporter genes shown in Tables 12A and/or 12B.
25. The method of claim 24, wherein the plurality of the 55 reporter genes comprises the 31 genes shown in Table 12A.
26. The method of claim 24, wherein the plurality of the 55 reporter genes consists of the 31 genes shown in Table 12A.
27. The method of any of claims 10 to 26, wherein the degree of similarity in step (d) is determined by calculating a correlation coefficient whose value is a known function of the similarity of the values of gene expression.
28. The method of claim 27, wherein the correlation coefficient is the Pearson correlation coefficient.
29. The method of claim 28, wherein if the Pearson correlation coefficient between the Mean NoCyR values of the 31 reporter genes of Table 12A and the measured values of gene expression of the same genes from a patient with a tyrosine kinase inhibitor drug responsive disorder is greater than or equal to 0.54 the patient is classified as a non-responder to treatment with a tyrosine kinase inhibitor drug and if the Pearson correlation coefficient between the Mean NoCyR values of the 31 reporter genes of Table 12A and the measured values of gene expression of the same genes from a patient with a tyrosine kinase inhibitor drug responsive disorder is less than 0.54 the patient is classified as a responder to treatment with a tyrosine kinase inhibitor drug.
30. The method of claim 28, wherein if the Pearson correlation coefficient between the Mean NoCyR values of the 31 reporter genes of Table 12A and the measured values of gene expression of the same genes from a patient with a tyrosine kinase inhibitor drug responsive disorder is greater than or equal to 0.57 the patient is classified as a non-responder to treatment with a tyrosine kinase inhibitor drug and if the Pearson correlation coefficient between the Mean NoCyR values of the 31 reporter genes of Table 12A and the measured values of gene expression of the same genes from a patient with a tyrosine kinase inhibitor drug responsive disorder is less than 0.57 the patient is classified as a responder to treatment with a tyrosine kinase inhibitor drug.

31. The method of any of claims 10 to 18, wherein the method of determining the levels of gene expression of two or more of the 55 reporter genes listed in Tables 12A and/or 12B in the sample from the patient comprises determining presence and levels of expression of the polypeptides corresponding to the two or more of the 55 reporter genes listed in Tables 12A and/or 12B.
32. The method of claim 31, wherein the presence and the levels of expression of the polypeptides of the said genes are detected by using a reagent which specifically binds to said polypeptides
33. The method of claim 32, wherein the reagent is selected from the group consisting of an antibody, an antibody derivative, and an antibody fragment.
34. The method of any of claims 31 to 33, wherein the presence and the levels of expression of the polypeptides of the said genes are detected through Western blotting using a labeled probe specific for each polypeptide.
35. The method of claim 34, wherein the labeled probe is an antibody.
36. The method of claim 35, wherein the antibody is a monoclonal antibody.
37. A method for determining the responsiveness of a patient with a tyrosine kinase inhibitor drug responsive disorder, to treatment with a tyrosine kinase inhibitor drug comprising:
 - (a) determining for the two copies of the putative gene DKFZP434C131 in the 15q22.33 region, present in the said patient, the identity of the nucleotide pair at the polymorphic site referred to as the rs2290573 polymorphism; and
 - (b) assigning the individual to a good responder group if both pairs are AT, or if one pair is AT and one pair is GC, and to a low responder group if both pairs are GC.
38. A method for determining the responsiveness of a patient with a tyrosine kinase inhibitor drug responsive disorder, to treatment with a tyrosine kinase inhibitor drug comprising:

- (a) determining for the two copies of the CYP1A1 gene, present in the said patient, the identity of the nucleotide pair at the polymorphic site at position 6819 in sequence X02612; and
- (b) assigning the individual to a good responder group if both pairs are AT, and to a poor responder group if both pairs are GC, or if one is GC and one is AT.
39. A method for determining the responsiveness of a patient with a tyrosine kinase inhibitor drug responsive disorder, to treatment with a tyrosine kinase inhibitor drug comprising:
- (a) determining for the two copies of the IL-1beta gene, present in the patient, the identity of the nucleotide pair at position 1423 of sequence X04500; and
- (b) assigning the individual to a good responder group if both pairs are CG, and to a poor responder group if one pair is AT and one pair is CG or if both pairs are AT.
40. The methods of any of claims 37 to 39 wherein the tyrosine kinase inhibitor drug responsive disorder is Philadelphia chromosome positive leukemia.
41. The methods of any of claims 37 to 40 wherein the tyrosine kinase inhibitor is Imatinib mesylate (Imatinib or GLEEVEC® or GLIVEC® or STI571).
42. A method according to any of claims 10 to 41, wherein said method is performed ex-vivo.
43. A kit for determining the responsiveness to treatment with a tyrosine kinase inhibitor drug of a patient with a tyrosine kinase inhibitor drug responsive disorder, comprising:
- a means for detecting the polypeptides corresponding to the two or more of the 55 reporter genes listed in Tables 12A and/or 3B.
44. A kit according to claim 43, wherein the means for detecting the polypeptides comprise antibodies, antibody derivatives, or antibody fragments.

45. A kit according to claim 43 or 44, wherein the polypeptides are detected through Western blotting utilizing a labeled antibody.
46. A kit according to any of claims 43 to 45, further comprising means for obtaining a biological sample of the patient.
47. A kit according to any of claims 43 to 46, further comprising a container suitable for containing the means for detecting the polypeptides and the biological sample of the patient.
48. A kit according to any of claims 43 to 47, further comprising instructions for use and interpretation of the kit results.
49. A kit for use in determining treatment strategy for a patient with a tyrosine kinase inhibitor drug responsive disorder, comprising:
- (a) a means for detecting the polypeptides corresponding to the two or more of the 55 reporter genes listed in Tables 12A and/or 12B;
 - (b) a container suitable for containing the said means and the biological sample of the patient comprising the polypeptides wherein the means can form complexes with the polypeptides;
 - (c) a means to detect the complexes of (b); and optionally
 - (d) instructions for use and interpretation of the kit results.
50. A kit for determining the responsiveness to treatment with a tyrosine kinase inhibitor drug, of a patient with a tyrosine kinase inhibitor drug responsive disorder; comprising:
- a means for measuring the level of transcription of the two or more genes listed in Tables 12A and/or 12B.
51. A kit according to claim 50, wherein the means for measuring the level of transcription comprise oligonucleotides or polynucleotides able to bind to the transcription products of said genes.

52. A kit according to claim 51, wherein the oligonucleotides or polynucleotides are able to bind mRNA or cDNA corresponding to said genes.
53. A kit according to any of claims 50 to 52, wherein the level of transcription is determined by techniques selected from the group of Northern blot analysis, reverse transcriptase PCR, real-time PCR, RNase protection, and microarray.
54. A kit according to any of claims 50 to 53, further comprising means for obtaining a biological sample of the patient.
55. A kit according to any of claims 50 to 54, further comprising a container suitable for containing the means for measuring the level of transcription and the biological sample of the patient.
56. A kit according to any of claims 50 to 55, further comprising instructions for use and interpretation of the kit results.
57. A kit for determining the responsiveness to treatment with a tyrosine kinase inhibitor drug, of a patient with a tyrosine kinase inhibitor drug responsive disorder; comprising:
- (a) a number of oligonucleotides or polynucleotides able to bind to the transcription products of the two or more genes listed in Tables 12A and/or 12B;
 - (b) a container suitable for containing the oligonucleotides or polynucleotides and the biological sample of the patient comprising the transcription products wherein the oligonucleotides or polynucleotide can bind to the transcription products;
 - (c) means to detect the binding of (b); and optionally
 - (d) instructions for use and interpretation of the kit results.
58. A method according to any of claims 10 to 42, wherein the determination step (b) further comprises the use a kit according to any of claims 43 to 57.
59. A kit for the identification of a polymorphic site of the putative gene DKFZP434C131 in the 15q22.33 region of a patient with a tyrosine kinase inhibitor drug responsive

disorder, said kit comprising a means for determining the genetic polymorphism pattern at the rs2290573CSK polymorphic site of the putative gene DKFZP434C131 in the 15q22.33 region.

60. A kit for the identification a polymorphism pattern at the CYP1A1 gene of a patient with a tyrosine kinase inhibitor drug responsive disorder, said kit comprising a means for determining the genetic polymorphism pattern at the CYP1A1 gene polymorphic site at position 6819 in sequence X02612.
61. A kit for the identification of a polymorphism pattern at the IL-1beta gene of a patient with a tyrosine kinase inhibitor drug responsive disorder, said kit comprising a means for determining the genetic polymorphism pattern at the IL-1beta gene at position 1423 in sequence X04500.
62. A kit according to claim 59, 60 or 61, further comprising a means for obtaining a biological sample of the patient.
63. A kit according to claim 62, wherein the means comprises a DNA sample collecting means.
64. A kit according to any of claims 59 to 63, wherein the means for determining a genetic polymorphism pattern at the specific polymorphic site comprise at least one gene specific genotyping oligonucleotide.
65. A kit according to any of claims 59 to 64, wherein the means for determining a genetic polymorphism pattern at the specific polymorphic site comprise two gene specific genotyping oligonucleotides.
66. A kit according to any of claims 59 to 65, wherein the means for determining a genetic polymorphism pattern at the polymorphic site comprise at least one gene specific genotyping primer composition comprising at least one gene specific genotyping oligonucleotide.
67. A kit according to claim 66, wherein the gene specific genotyping primer composition comprises at least two sets of allele specific primer pairs.

68. A kit according to claim 67, wherein the two allele specific genotyping oligonucleotides are packaged in separate containers.
69. A method according to any of claims 37 to 42, wherein the determination step (a) further comprises the use a kit according to any of claims 50 to 57.